PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
W. Antoni Kudlicki
Matthew M. Winkler and
Brittan L. Pasloske

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Examiner: A. Chakrabarti

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CERTIFICATE OF MAILING
37 C.F.R. § 1.8

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December 19, 2002
Date

Mark B. Wilson

I. STATEMENT OF SUBSTANCE OF INTERVIEW; II. AMENDMENT; AND III. RESPONSE TO OFFICE ACTION DATED SEPTEMBER 19, 2002

Commissioner for Patents
Washington, D.C. 20231

Sir:

This paper is submitted in response to the Office Action dated September 19, 2002 ("the Action"), for which the three-month date for response is December 19, 2002. No fee is believed due; however, should any fee be required please consider this paragraph a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/AMBI:052US.

Reconsideration of the application is respectfully requested.

I. STATEMENT OF SUBSTANCE OF EXAMINER INTERVIEW OF OCTOBER 24, 2002

Applicants thank Examiner Chakrabarti for the courtesies extended during the interview of October 24, 2002. Applicants herein provide a statement of the substance of the interview under 37 C.F.R. 1.133(b).

The interview was attended by Examiner Chakrabarti and Applicants' representatives Thomas M. Boyce and Michael Krawzsenek (Reg. No. 51,898). Examiner Chakrabarti began by expressing his opinion that if the "first" rejection under 35 U.S.C. §103(a) were to be overcome (*i.e.,* Item 4, page 3, of the Office Action of September 19, 2002), the remaining rejections under §103(a) would also be overcome.

With respect to the rejections under §103, Mr. Boyce asked for clarification of the content and relevance of the Cazenave reference (Cazenave, P.-A., Proc. Natl. Acad. Sci. USA 74:5122-5125, 1977). In particular, Mr. Boyce asked whether the Cazenave reference discloses antibodies to RNAse 1. Upon further reading of the reference and discussion, Examiner Chakrabarti agreed that Cazenave (1977) does not disclose anti-RNAse 1 antibodies. Additionally, Mr. Boyce asked for clarification as to whether the Cazenave reference discloses antibodies to micrococcal nuclease. Upon further reading and reflection, Examiner Chakrabarti agreed that the antibodies to micrococcal components discussed in Cazenave on page 5124 of the reference are anti-carbohydrate antibodies and not anti-nuclease antibodies.

Examiner Chakrabarti indicated that since the Cazenave reference appears to not disclose anti-RNAse 1 antibodies, claim 56 and its dependent claims are allowable in their present condition, in the absence of any additional prior art that may disclose an anti-RNAse 1 antibody.

With respect to the remaining claims, Examiner Chakrabarti requested clarification of the scope of claims 1 and 47,[1] inquiring as to whether the recited first soluble anti-nuclease antibody and second soluble anti-nuclease antibody were antibodies directed to different nucleases. Examiner Chakrabarti suggested that if that were the case, the claim should be amended to reflect that limitation. Mr. Boyce agreed to obtain the advice of the Applicants on that matter and to so amend the claims if appropriate.

II. AMENDMENT

In the Claims:

Please amend the claims as follows:

1. (Amended Three Times) A method comprising:

   a) obtaining at least a first soluble anti-nuclease antibody;

   b) obtaining at least a second soluble anti-nuclease antibody wherein said first and said at least second soluble anti-nuclease antibodies bind to different nucleases;

   c) obtaining a composition; and

   d) admixing the anti-nuclease antibodies and the composition to form an admixture;

wherein nucleases that may be present in the admixture are inhibited.

47. (Amended) The method of claim 45, wherein the second nuclease inhibitor is a second soluble anti-nuclease antibody wherein said first and said second soluble anti-nuclease antibodies bind to different nucleases.

[1] Applicants note that the Interview Summary provided by Examiner Chakrabarti refers to claim 37 in this respect. However, Applicants respectfully submit that this is a typographical error since the relevant claim limitations appear in claim 47.

The claims marked for amendment are provided in Appendix A. For the Examiner's convenience, a clean copy of the pending claims as they stand amended is provided in Appendix B.

III. RESPONSE

A. Status of the Claims

Claims 1-50 were filed with the application. Claims 1-23 and 37-49 were elected in response to the restriction requirement of September 14, 2001. Claims 8, 17 and 22 have been previously canceled without prejudice or disclaimer. Claims 1-7, 9-16, 18, 20, 23, 44 and 46 were amended and new claims 51-55 added by the amendment filed February 7, 2002. Claims 1 and 47 are amended herein. Therefore, claims 1-7, 9-16, 18-21, 23, 37-49, and 51-66 are presently pending.

B. The Rejections Under 35 U.S.C. 103(a) Are Overcome

The Action rejects all of the claims as obvious in view of Lee *et al.*, in combination with one or more of Cazenave, Bucala *et al.*, Murphy *et al.* and Trent *et al.* (Journal of General Virology 47:261-82). Applicants respectfully traverse these rejections.

1. The claim limitations are not to be found in the cited art.

Applicants respectfully note that all the rejections under 35 U.S.C. §103(a) are premised upon the alleged disclosure of anti-RNAse 1 antibodies in the Cazenave (1997) reference. *See,* Action, pg. 3, ln. 6; pg. 6, ln. 18; pg. 8, ln. 6; pg. 10, ln. 17; and pg. 12, ln. 18.

As Applicants have previously argued in their submissions of February 7, 2002, and July 19, 2002, a proper reading of the Cazenave reference reveals that it does not disclose equivalent second and third nuclease inhibitors as anti-ribonuclease antibodies as asserted by the Action.

There are, in fact, no mixtures of anti-RNase 1 antibodies disclosed by Cazenave, nor any mention of Micrococcal anti-ribonuclease. This fact has been verified by the clarification of the content of the Cazenave (1997) reference kindly provided by the Examiner in the interview of October 24, 2002, which clearly indicates that Cazenave does not disclose anti-RNAse 1 antibodies nor Micrococcal anti-nuclease antibodies (see Statement of Substance of Interview, above).

Cazenave, therefore, does not disclose the limitations of the claims that are absent from the balance of the references cited in the present rejections.

Similarly, a proper reading of Trent *et al.* reveals that its text nowhere discloses an anti-RNAse T1 antibody. Indeed, the passage quoted in the Action from Trent *et al.* is instructive on this point because it clearly indicates that the disclosure of Trent *et al.* bears no relation to anti-RNAse T1 antibodies at all. Rather, Trent *et al.* disclose in the passages quoted in the Action that "long T1 oligonucleotides of WEE and HJ viruses are chemically unique."

Respectfully, Applicants point out that oligonucleotides, *i.e.* polynucleotides (RNA in Trent *et al.*) are not proteins nor antibodies. Trent *et al.* simply do not disclose anti RNAse T1 antibodies, which, as is known to those of skill in the art, are proteins that react antigenically with their target antigen. Rather, Trent *et al.* disclose a procedure that digests polynucleotides with the enzyme RNAse T1 in order to generate a "fingerprint" based upon the chemical differences between polynucleotides generated by RNAse T1 digestion. Trent *et al.*, page 262, last paragraph of introduction and the sections entitled "Nuclease digestion of RNA and separation of oligonucleotides by two-dimensional electrophoresis" and "Extraction and characterization of oligonucleotides" at the middle of page 264. Also see the section entitled

"Comparison of the oligonucleotides of WEE and HJ virus isolates" beginning at the bottom of page 269 and extending through the bottom of page 278.

As is clear from a thorough reading of the Trent *et al.* reference, the sole use of any antibodies disclosed by Trent *et al.* is in the characterization of viral envelope glycoproteins. See Trent *et al.* bottom of page 264 through page 265. But as is well known to those of skill in the art, viral envelope glycoproteins are not comprised of RNAse T1. Therefore, the disclosure of Trent *et al.* does not provide any disclosure that could render any of the present claims obvious.

Applicants therefore respectfully submit that all the rejections of the Action are improper under 35 U.S.C. §103(a) because the cited references (in particular, Cazenave (1997) and Trent *et al.* (1980)) do not disclose the limitations of the present claims. As argued in Applicants' previous submissions, the cited art as a whole does not suggest or disclose all the elements of the presently claimed invention. Applicants therefore respectfully request reconsideration and withdrawal of the rejections.

With respect to each asserted rejection, Applicants provide the following additional and specific arguments.

a. The rejection of claims 1-5, 7, 9, 10, 12, 13, 15, 16, 18, 20 and 23 is overcome.

The Action rejects the claims as obvious over Lee *et al.* in view of Cazenave. Applicants respectfully traverse.

The Action admits that Lee *et al.* do not teach the method of claim 1, which provides for a second, soluble anti-nuclease antibody, which binds to a different nuclease from the first soluble anti-nuclease antibody. Action, page 4. The rejection is grounded on the alleged disclosure of Cazenave of a second soluble anti-nuclease antibody. However, as discussed

above, Cazenave neither discloses nor suggests such an antibody. Therefore, the cited references together, taken as a whole, do not disclose all of the claim limitations of claim 1 and its dependent claims.

Applicants therefore respectfully request reconsideration and withdrawal of the rejections.

b. The rejection of claims 11, 14, and 19 is overcome.

The Action rejects claims 11, 14, and 19 as obvious over Lee *et al.* in view of Cazenave and in further view of Bucala *et al.* Applicants respectfully traverse. As argued above, the combination of the Lee *et al.* and Cazenave references does not render the claims obvious because they do not disclose or suggest all of the claim limitations. Claims 11, 14, and 19 incorporate these non-obvious limitations and are therefore themselves non-obvious.

Furthermore, claims 11, 14, and 19 recite at least in part the limitation of an anti-RNase A antibody. The Action admits that Lee *et al.* and Cazenave do not disclose the presently claimed methods wherein the anti-ribonuclease antibody is an anti-RNase A antibody. Nevertheless, the Action suggests that one of skill in the art would be motivated to combine the anti-RNase antibody of Bucala *et al.* (2000) with the alleged teachings of Lee *et al.* and Cazenave to result in a method of inhibiting nucleases.

But contrary to the argument of the Action, RNase activity, *per se*, is never at issue in the Bucala *et al.* reference. Indeed, the quoted passage from Bucala *et al.* itself expressly teaches away from such a combination. In the Bucala *et al.* reference, RNase proteins are described merely as indicators of the extent of dimerization promoted by glycotoxins. Bucala *et al.* used rabbit anti-RNase A antibodies conjugated to HRP to detect ***denatured*** RNase proteins in a western blot. Bucala *et al.* therefore expressly did not use anti-RNase A antibodies effective in inhibiting active RNase activity.

The Action cites Bucala *et al.* for the disclosure of an anti-RNase A antibody. However, as discussed above, there is no disclosure in Bucala *et al.* that the antibodies of Bucala *et al.* would be effective to inhibit nuclease activity since the RNase proteins detected by the antibodies of Bucala *et al.* were already denatured, that is, they had no activity to inhibit. Thus, Bucala *et al.* in conjunction with Lee *et al.* does not enable the use of soluble anti-RNase A antibodies to inhibit the activities of active nucleases in solution and cannot support a *prima facie* case of obviousness against the claims.

c. The rejection of claims 6, 37-49, and 51-55 is overcome.

The Action rejects claims 6, 37-49, and 51-55 as obvious over Lee *et al.* in view of Cazenave, Bucala *et al.*, and Murphy *et al.* Applicants respectfully traverse.

First, Applicants respectfully note that claim 6 incorporates the non-obvious limitations of claim 1 and therefore is itself non-obvious.

Applicants respectfully submit that no *prima facie* case of obviousness has been made against the claims because Murphy *et al.* leads the artisan away from the present invention because Murphy *et al.* counters any reasonable expectation of success. Applicants therefore submit that the rejections are overcome.

Applicants agree with the arguments of the Action to the extent that Lee *et al.* in view of Cazenave do not disclose or suggest the limitations of claims 37-49 and 51-55, which contain the express limitations of a method of performing an in vitro translation. Applicants also agree that Lee *et al.* in view of Cazenave do not disclose or suggest human placental ribonuclease inhibitor. But further, as argued previously, Lee *et al.* in view of Cazenave do not disclose or suggest a method of performing in vitro translation comprising obtaining a first nuclease inhibitor, which inhibitor is

further defined as a soluble anti-nuclease antibody, and placing the anti-nuclease antibody in an *in vitro* translation reaction.

Nor does Murphy *et al.* provide any suggestion of the presently claimed methods. Murphy *et al.* does not disclose the use of any antibodies whatsoever, and most especially not in *in vitro* translation reactions. Furthermore, there is no suggestion in Lee *et al.* that antibodies would work to remove nucleases from an *in vitro* transcription or other reaction mixture beyond that disclosed by Lee, *i.e.*, crude tissue homogenates. And, Lee *et al.* in view of any of the cited references does not provide for soluble anti-nuclease antibodies effective as inhibitors of nucleases. Therefore, there is no basis for an artisan of ordinary skill to conclude from these references that the addition of soluble anti-ribonuclease antibodies to a reaction mixture such as an *in vitro* transcription reaction would perform as desired.

In fact, Murphy *et al.* disclose that "An extremely important feature of a RNase inhibitor" for use in such reactions is "that it remain fully functional under the various conditions to which RNA may be subjected." See Murphy *et al.*, under "Reaction Parameters," first paragraph, lines 1-3. Yet, there is no demonstration or suggestion in any of Lee *et al.* or Murphy *et al.* that anti-ribonuclease antibodies could withstand the various conditions as disclosed in the Murphy *et al.* reference and be effective to inhibit nucleases. Absent such a suggestion from any reference and from the knowledge of one of skill in the art, Murphy *et al.* only teaches away from the present invention. Murphy *et al.* raises numerous barriers to be crossed before achieving a successfully useful RNase inhibitor rather than enabling the ordinary artisan to make and use the present invention as claimed. That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness, even if all the elements of the invention are shown to be available in the art. *Winner Int'l. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000).

Additionally, and as argued previously in this case, none of the references alone or in combination provide or suggest the specific limitations of these rejected claims. Here, in particular, Applicants point out that the method of claim 54, which expressly recites the use of three anti-nuclease antibodies in an *in vitro* translation--an anti-RNase A antibody, an anti-RNase 1 antibody, and an anti-RNase T1 antibody--is nowhere disclosed or suggested in the art.

Applicants note that claim 51 recites the inclusion of at least a third anti-nuclease antibody, which binds to one or more of RNase A, a member of the RNase A family, RNase B, RNase C, RNase 1, RNase T1, RNase T2, RNase L, a member of the RNase H family, a member of the angiogenin RNase family, eosinophil RNase, a micrococcal nuclease, a member of the mammalian ribonuclease 1 family, a member of the ribonuclease 2 family, a messenger RNA ribonuclease, 5'-3' exoribonuclease, 3'-5' exoribonuclease, a decapping enzyme, a deadenylase, RNase P, RNase III, RNase E, RNase I,I*, RNase HI, RNase HII, RNase M, RNase R, RNase IV, F; RNase P2,O, PIV, PC, RNase N, RNase II, PNPase, RNase D, RNase BN, RNase T, RNase PH, OligoRNase, RNase R, RNase Sa, RNase F1, RNase U2, RNase Ms, or RNase St. But nowhere in the cited references is there to be found the suggestion or provision of at least a third anti-nuclease antibody as claimed.

Claim 55 recites the express limitation that RNA be produced in the admixture of the method comprising at least a first soluble anti-nuclease antibody, obtaining at least a second soluble anti-nuclease antibody, obtaining a composition, and admixing the anti-nuclease antibodies and the composition to form an admixture comprising RNA, wherein nucleases that may be present in the admixture are inhibited. Applicants have seen nothing in the record or in the text of the rejections as stated that suggest that claim 55 is present in or obvious over the art.

Applicants respectfully submit that no *prima facie* case of obviousness has been made against the claims. Applicants therefore submit that the rejections are overcome.

d. The rejection of claims 56-60, 61 and 62-66 is overcome.

The Action rejects claims 56-60 and 62-66 as obvious over Lee *et al.* in view of Cazenave, Bucala *et al.* and further in view of Trent *et al.* Applicants respectfully traverse.

The grounds for the asserted rejection rest upon the interpretation of the disclosure of Trent *et al.* as providing for antibodies to RNAse T1. But, as discussed above, the text of Trent *et al.* nowhere discloses such antibodies. Therefore, the reliance of the rejection upon the disclosure of Trent *et al.* is misplaced, and no *prima facie* case of obviousness can be made against the claims based upon Trent *et al.*

Furthermore, the rejected claims expressly provide for antibodies to RNAse 1 (among other elements). As discussed above, there is no disclosure in the cited references of antibodies to RNAse 1 in Cazenave or any of the other references.

In view of the lack of any disclosure of at least two express claim limitations in these rejected claims, Applicants respectfully submit that no *prima facie* case of obviousness has been made. Applicants therefore respectfully request reconsideration and withdrawal of the rejections.

2. There is no suggestion in the cited art to make the present invention with any reasonable expectation of success.

Even if the cited references contained sufficient disclosure or suggestion of all of the claimed elements of the present invention, Applicants continue to respectfully maintain that the cited references are devoid of the requisite teaching of an expectation of success in making the present invention. Therefore, no valid *prima facie* case of obviousness has been made. Applicants therefore respectfully request reconsideration and withdrawal of the rejections.

The Action argues that Lee *et al.* provides "strong motivation" to make and use the present invention, citing the passage of Lee *et al.* suggesting improvements in the methods of purification of polysomes. Applicants respectfully point out that any suggestion to combine the teachings of references must be accompanied by a reasonable expectation of success. Applicants have not found either the required suggestion to make and use the present invention nor the requisite reasonable expectation of success in the sum of the references cited.

Applicants respectfully submit that Lee *et al.* teach away from the present invention. The anti-nuclease antibodies contemplated by Lee *et al.* are necessarily insolubilized. Lee *et al.* expressly do not use soluble antibodies, nor does the text suggest that soluble antibodies would be effective or useful in any of their disclosed or suggested methods. The methods disclosed by Lee *et al.* employ antibodies to rabbit spleen RNase (r-s-RNase) as a "reverse immunosorbent, prepared by polymerizing monospecific sheep antibodies to r-s-RNase with ethylene-maleic anhydride copolymer (EMA)." Lee *et al.*, pg. 210, lns. 25-26, through pg. 211, ln. 1, internal quotes and referenced omitted. Thus, the antibodies disclosed by Lee *et al.* are rendered insoluble.

The necessity of insoluble antibodies to the methods of Lee *et al.* is made clear by the statement of prior success by Lee *et al.* in that "[t]his immunosorbent was shown to be capable of ***removing*** completely any free r-s-RNase (Lee and Sehon, 1971)." Lee *et al.* pg. 211, lns. 2-3, (emphasis added). It is thus clear from the disclosure of Lee *et al.* that the methods contemplated are for removing nucleases from solution by their binding to insolubilized antibodies, *i.e.* the so-called reverse immunosorbents. Furthermore, the suggestion by Lee *et al.* to further improve the methods of polysome isolation contemplate not the addition of soluble anti-nuclease antibodies, but the use of additional, insolubilized antibodies, which would act in the same manner as

disclosed for the anti r-s-RNase antibodies in removing the nucleases from solution. Lee *et al.* pg. 213, lns. 3-7.

Even if the disclosure of Lee *et al.* is read in the most favorable light, the disclosure does not provide any data or reasoning to support the speculation that use of a mixture of ***soluble antibodies*** would be effective in achieving the present invention. Contrary to that speculation, Lee *et al.* expressly indicate that removal of the nucleases from solution is the means by which improved polysome isolation is achieved. That such removal is central to the methods of Lee *et al.* is indicated in part by the suggestion of Lee *et al.* that in order to achieve improved polysome isolation, the additional, polyspecific antibodies would have to be cross-linked with EMA to form a "polyspecific immunosorbent," which would then be expected to result in improved yields of polysomes. But more importantly, there is no data or suggestion in Lee *et al.* that the use of soluble anti-nuclease antibodies would work to inhibit nucleases as presently claimed.

Therefore, not only does Lee *et al.* not provide the requisite suggestion to combine, coupled with a reasonable expectation of success, its suggestion, read in light of its full text, Lee *et al.*, actually teaches away from the present invention, which expressly recites soluble anti-nuclease antibodies as effective inhibitors of nucleases. That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness, even if all the elements of the invention are shown to be available in the art. *Winner Int'l. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000).

Nor does the balance of the references suggest the present invention or overcome the teaching away of Lee *et al.* As explained in Applicants' previous response and as reiterated here, Cazenave is not concerned with the use of anti-nuclease antibodies to inhibit nucleases. Indeed,

Cazenave is not concerned with nuclease activity at all, but rather the transfer of idiotypes from one episode of immunization to another. As explained previously and below, the unspecified RNase antigens of Cazenave are the only primary antigens used in creating antibodies Ab1 and, independently, Ab1′. The rest of the antigens used are antibodies themselves. At best, Cazenave discloses that antibodies to some unspecified RNase can be made. But even so, no disclosure or suggestion that any of these antibodies would be effective in inhibiting nucleases is provided.

Bucala *et al.*, as explained previously and below, is not concerned with the binding of anti-nuclease antibodies to active nucleases at all. In fact, all the nucleases bound to antibodies disclosed in Bucala *et al.* are ***already denatured*** through electrophoresis under reducing conditions. Therefore, no inference that the antibodies used by Bucala *et al.* could or would in fact inhibit any nuclease activity may be gleaned from its disclosure. Murphy *et al.*, though expressly addressing the use of RNase inhibitors in various reaction conditions, does not disclose or discuss the use of any antibodies whatsoever.

The disparate objectives and disclosures of the cited references thus do not come together to suggest to the ordinary artisan that one may make and practice the present invention, which is expressly directed to the inhibition of nuclease activity through methods employing at least two soluble anti-nuclease antibodies. No fair reading may find a suggestion of the present invention in the sum of the disclosures of the cited references. Indeed, Lee *et al.* and Bucala *et al.* teach away from the present invention. Applicants therefore respectfully submit that no *prima facie* case of obviousness has been made. Applicants therefore respectfully request that the rejections be withdrawn.

CONCLUSION

In light of the foregoing amendments and remarks, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a call to the undersigned is invited.

Respectfully submitted,

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